Claims 6 through 13 were pending in the present application, claims 10-13 have been canceled, and the remaining claims amended. Accordingly, claims 6 through 9 remain pending in this application. Reconsideration of the outstanding rejections and allowance of claims 6 to 9 are hereby requested.

THE ANTICIPATION REJECTION

Claims 7-9 stand rejected under 35 USC §1.102(b) or in the alternative under 35USC §102(a), allegedly as being anticipated by Deckmann. This ground of rejection is traversed.

Deckmann is different from the claimed invention, and fails to render it obvious. The Deckmann reference relates to a diagnostic method for determining schizophrenia in a subject by comparing a non-schizophrenic control and a patient with schizophrenia. The method comprises obtaining a preparation comprising platelet derived proteins from self, injecting the preparation into a subject and examining the subject for the occurrence of delayed type hypersensitivity reaction at the site of injection and positive reaction at the site of injection indicating that the subject has a high likelihood of being schizophrenic. However, the characteristics employed by Deckmann differ from the claimed reagent, and fail to render it obvious. In similar manner the prior art reference fails to show all the elements of claims 7 through 9.

Claim 1 is directed to a method for preparation of a reagent for use in diagnosis of schizophrenia that comprises obtaining blood samples from a number of individuals, and preparing a pool and collecting platelets therefrom; preparing a protein fraction from the platelet preparation that has proteins or fractions thereof having a pI of about 6.5 to about 9.5. The thus obtained platelet preparation is then injected into a subject; and the occurrence of a DTH reaction at the site of injection observed. If the DTH reaction at the site of injection is greater than that observed in a non-schizophrenic subject under similar conditions the reaction is considered positive, and it may be said that the subject has a high likelihood of being schizophrenic. In similar manner, claims 7 through 9 have the same requirements listed by claim 6 regarding the steps and characteristics of its reagent.

. Nor does the prior art suggest to an artisan the path between its method and reagents and the claimed methods. The Deckmann reference fails to provide all the elements of the methods of claims 6-9.

THE FIRST OBVIOUSNESS REJECTION

Claims 6-13 stand rejected under 35 USC §1.103(a), as being unpatentable over Deckmann in view of WO 97/13152 (WO '152) and Rotman. This ground of rejection is traversed.

In order to establish a prima facie case of obviousness the PTO must satisfy three requirements. First, the prior art reference must teach or suggest all the limitations of the claims. In re Wilson, 424, F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Second, the prior art relied upon, coupled with the knowledge

generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Third, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). The outstanding rejection meets none of these requirements.

The combination of Deckmann with WO 97/13152 and Rotman fails in establishing a prima facie case of obviousness as well.

Deckmann was discussed above, as were the reasons why it neither anticipates nor renders the claimed methods obvious.

WO '152 is also different from the claimed invention, and fails to provide the missing link in the Deckmann publication. WO '152 discloses an assay for the diagnosis of dementia and Alzheimer's disease, involving determination of the level of a 75 kD platelet protein and platelet-associated antibodies ("PAA") to the 76 kD protein. WO 97/13152 neither discloses nor suggests that platelet proteins might be useful in an assay for schizophrenia and, therefore, fails to make up for the Deckmann defficiencies.

Rotman is also different from the claimed invention and, as WO '152 before, fails to provide the missing link in Deckmann that would lead an artisan to the claimed invention. Rotman discloses that platelets may be used as a tool for testing neuropharmaceuticals and are a good model for serotonin and imipramine uptake by neuronal tissues, **not of dopamine or norephinephrine**. More specifically, Rotman discloses that the Km for platelet serotonin uptake in normal and schizophrenic subjects is unchanged, while the Vmax for schizophrenic subjects is 35-40% lower than normal subjects. In addition, Rotman also discloses the existence of a correlation between a decrease in the number of α-adrenergic receptors and the incidence of schizophrenia. Applicants respectfully submit that this data, showing the same individual transporter kinetics but lower overall transport, demonstrates that there are simply fewer serotonin transporters and α-adrenergic receptors in schizophrenic subjects. Further, Rotman also suggests that platelet shape changes are correlated with serotonin uptake and perhaps neuronal disorders.

However, what Rotman fails to either disclose or suggest is that there is any correlation between the number of normal serotonin transporters and α-adrenergic receptors, and the number or platelet proteins or the quantity of antibodies to such proteins. Indeed, it is counter-intuitive to interpret Rotman as suggesting that one of ordinary skill in the art would expect an enhanced immune response to fewer transporters without a specific teaching to that effect. Nor does Rotman teach or suggest that shape changes in platelets are in any way related to an enhanced immune response; again, it is counter-intuitive to reach such a conclusion without a specific teaching to that effect. Moreover, whether or not Rotman teaches that platelets are a good tool for testing

neuropharmaceuticals is irrelevant to the presently claimed invention, which is directed to the diagnosis – not treatment – of schizophrenia.

In the absence of all the elements for substantiating a prima facie case of obviousness, this ground of rejection fails. Therefore, the examiner is invited to withdraw this rejection.

THE SECOND OBVIOUSNESS REJECTION

Claims 6-13 stand rejected under 35 USC §1.103(a) as being unpatentable over Jankovic in view of WO 97/13152 (WO '152), Ovary and Rotman. This rejection is also traversed.

The combination of Jankovic with WO '152 and Ovary fails. Neither Jankovic alone, nor its combination with WO '152 and/or Ovary disclose or suggest the claimed methods.

Jankovic is different from the claimed invention, and fails to suggest a path that would lead an artisan to the claimed invention. Jankovic disclose a correlation between several psychiatric disorders and skin hypersensitivity to brain S-100 protein and to neuron-specific enolase ("NSE"), as a result of the presence of circulating antibodies to these two proteins. See, Tables 1 and 2 of Jankovic. Jankovic also makes the broad statement that there is a correlation between immunopsychiatric disorders and delayed hypersensitivity to neural tissue antigens generally. However, ***Jankovic neither diclose nor suggest that the level of platelets or platelet associated antibodies is in any way related to psychiatric disorders***. There is neither mention nor a suggestion in the prior art reference that (1) platelets are neural tissue, or that (2) platelet associated antibodies are neural tissue antibodies. Nor did the art in general disclose or suggest these concepts at the time of the claimed invention. Indeed, a general understanding of what platelets are and neural tissues are would teach away from the claimed invention. Such understanding would even lead one of ordinary skill to the conclusion that they are not related in any way, at least in the absence of some teaching or suggestion to the contrary.

The combination of Janovic with WO '152, Rotman and Ovary fails as well. Neither WO '152, nor Rotman or Ovary cure the deficiencies of the Jankovic reference. WO '152 was discussed above as were the reasons why it neither anticipates nor renders the claimed methods obvious. WO '152 is different from the claimed invention, and fails to cure the deficiencies of Jankovic. WO '152 discloses an assay for the diagnosis of dementia and Alzheimer's disease by determination of the level of a 75 kD platelet protein and platelet-associated antibodies ("PAA") to the 76 kD protein. WO 97/13152 neither discloses nor suggests that platelet proteins might be useful in an assay for schizophrenia and, therefore, fails to provide the missing link from Jankovic to the claimed methods.

Rotman is also different from the claimed methods, and fails to cure the deficiencies of Jankovic and/or WO '512. Rotman discloses platelets as a tool for testing neuropharmaceuticals, and described them as a good model for the uptake by neuronal tissues of serotonin and imipramine,

but not dopamine or norepinephrine. More specifically, Rotman teaches that the Km for platelet serotonin uptake in normal and schizophrenic subjects is unchanged, while Vmax for schizophrenic subjects is 35-40% lower than normal subjects. Similarly, Rotman teaches that there is a correlation between a decrease in the number of α-adrenergic receptors and the incidence of schizophrenia. This data relates to the same individual transporter kinetics but lower overall transport and, necessarily, demonstrates that there are simply fewer serotonin transporters and α-adrenergic receptors in schizophrenic subjects. Further, Rotman also suggests that platelet shape changes are correlated with serotonin uptake and perhaps neuronal disorders.

Rotman neither teach nor suggest that there is any correlation between the number of normal serotonin transporters and α-adrenergic receptors, and the number of platelet proteins or the quantity of antibodies to such proteins. Indeed, it is counter-intuitive to interpret Rotman as suggesting that one of ordinary skill in the art would expect an enhanced immune response to fewer transporters without a specific teaching to that effect. Nor does Rotman teach or suggest that shape changes in platelets are in any way related to an enhanced immune response; again, it is counter-intuitive to reach such a conclusion without a specific teaching to that effect.

Ovary is also different from the claimed methods, and fails to cure the deficiencies of Jankovic either alone or its combination with WO '152 and/or Rotman. Ovary discloses only that the skin is a good milieu for the study of delayed hypersensitivity responses. Ovary neither disclose nor suggest that platelet proteins might be useful in an assay for schizophrenia.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art reference must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

This standard has not been met. Thus, the combination of Jankovic with WO '152 and/or Rotman and/or Ovary clearly fails. None of the cited references, wither by itself or in combination, teach all elements of the inventive subject matter. The references of record fail to substantiate a prima facie case of obviousness for the claimed invention. The examiner is therefore invited to withdraw this rejection as well.

The examiner's attention is directed to the fact that of record in this case is the Shinitzky declaration. Dr. Meir Shinitzky, one of the present inventors, is also a co-inventor in WO '152 and a co-author of the Kessler publication, and has personal knowledge of the work described in the Burbaea/Jankovich publication. In the Declaration, Dr. Shinitzky described in detail the work relating to WO '152. In brief, WO '152 clearly states that the 75 kD platelet-protein and the related platelet associated antibodies, associated with multi-infarct dementia and dementia of the Alzheimer type, are mot the same as the isolated platelet-proteins or fractions thereof having a pI above about 6.5. The latter are the subject of the claimed invention.

The examiner states that the Shinitzky declaration is insufficient to overcome this rejection. However, he provided no contrary evidence or reasoning for the refusal to accept an expert's Declaration under oath, which expert, by being an inventor as well, has first hand knowledge of the facts stated therein. The USPTO should not be in the business of questioning, let alone rejecting, an expert's Declaration without substantive and critically related evidence. ***Contrary to the examiner's arguments, the undisputed evidence before the us shows that WO '152 teaches the use of different proteins for screening for a different disorder, and thus teaches nothing whatsoever about the claimed inventive subject matter***.

THE INDEFINITENESS REJECTION

Claims 6-10 stand rejected under 35 USC §1.112, second paragraph, as being indefinite. This rejection is traversed.

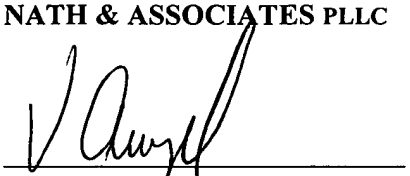
Claims 10-13 have been canceled, and the remaining claims amended along the lines of the examiner's suggestions. The pending claims have been amended to refer to a range of pI of about 6.5 to about 9.5 . The applicant believes the pending claims to be free of this ground of rejection.

THE CLAIM AMENDMENTS

The claims have been amended to place them in proper US form and to better describe the claimed invention. No objectionable new matter is believed to have been incorporated by the present amendments.

In view of the above remarks the pending claims are believed to be in condition for allowance. Prompt notice to that effect is solicited by the applicant.

Respectfully submitted,
NATH & ASSOCIATES PLLC



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